



Stem Cells Intended for Cosmetic Use Only: Regulation in Belgium, Europe and the United States

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**STEM CELLS INTENDED FOR COSMETIC USE ONLY:
REGULATION IN BELGIUM, EUROPE AND THE UNITED STATES**

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ABSTRACT

The central question in this paper is whether it is wise to assume that cosmetics are not hazardous, especially in the light of the stem cell hype. Some cosmetics contain stem cell extracts or claim to influence the stem cells in the skin. This paper examines the issue of these “stem cell creams” in three jurisdictions: Belgium, Europe and the United States.

The paper approaches the issues raised by the advent of such products in the following manner: first, the classification problem is discussed. Stem cell creams sometimes fall in a grey area between cosmetics and drugs. When the categorization is only based on claims made of the products, manufacturers can easily evade their responsibilities by manipulating the claims.

The applicable regulations are then analyzed. Although the requirements for drugs are similar in the three jurisdictions, this is not the case with respect to cosmetics. Cosmetics are clearly regulated more strictly in Europe. Finally, a clear overview of the loopholes in the current regulations is offered and some recommendations for change are proposed. The conclusion of the paper is that the discussed stem cell creams might be hazardous and therefore, should be rigorously regulated. Moreover, something as superficial as claims by manufacturer should not be determinative so as to alter the classification of a product. The European model could thus arguably be an inspiration for FDA to base future reforms upon.

STEM CELLS INTENDED FOR COSMETIC USE ONLY:
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Introduction

Today when purchasing a cosmetic one expects that the product will cause no harm. In the past, nevertheless, some cosmetics such as lead-based pigments were quite hazardous to people's health.¹ The danger led to the regulation of cosmetics. Because of this regulation, people are convinced that the safety of their cosmetics is assured. However, in light of new scientific breakthroughs, cosmetics are not what they used to be anymore. The central question of this paper is whether it is wise to assume that cosmetics are not hazardous. The paper examines this issue in three jurisdictions: Belgium, Europe and the United States.

Nowadays many cosmetic companies use extracts of stem cells in their products and refer even to them in their labels and advertisements. At the end of 2010, the California-based International Stem Cell Corporation started selling anti-aging products in the U.S. developed by its subsidiary Lifeline Skin Care. These moisturizers contain patented, non-embryonic (parthenogenetic²) human stem cell extracts.³ Another skin care product is called Stemixx and is manufactured by Californian AmStemInc.⁴ This anti-wrinkle cream is a reformulated version of a Stem Cell Facial Cream, which has been sold in Korea under the label "97.7" for over two years. The main ingredient is listed as "HSCM," an abbreviation for Human Stem

¹ Charles I. Betton, *Risk Assessment and Cosmetics*, in 1 GLOBAL REGULATORY ISSUES FOR THE COSMETICS INDUSTRY 1, 10 (Charles I. Betton ed., 2007).

² Parthenogenesis creates pluripotent human stem cells from unfertilized oocytes. This is not explained on the website of the company. However e.g. Press Release, *ISCC Announces Successful Manufacture of New Anti - Aging Stem Cell - Based Product Line*, SPECIALCHEM, Oct 27, 2010, <http://www.specialchem4cosmetics.com/services/news.aspx?id=5750>

³ <http://www.lifelineskincare.com/>

⁴ <http://www.amsteminc.com/amstem-products/stemixx-facial-cream/>

Cell Conditioned Media Extract, which is composed of nutrients and proteins secreted during the culture of stem cells derived from human umbilical cord blood.

Other creams do not contain human stem cell extracts but nevertheless claim to influence the skin's stem cells. Examples are Lancôme's Absolue Precious Cells,⁵ Amatokin Emulsion by Voss Laboratories,⁶ ReVive's Peau Magnifique,⁷ Dior's Capture R60/80 XP,⁸ Emerge Swiss Apple Stem cell serum,⁹ StemCellin Intensive Emulsion and StemCellin Deep Wrinkle Serum¹⁰.

Stem cells are clearly hyped and businesses are keen to take advantage of the perceived value of stem cells to positively affect their bottom line. In this paper I will discuss first how creams that are said to influence the user's own stem cells are classified in Europe and in the U.S. Then I will focus on the classification of creams containing stem cells or stem cell extracts. After that, I will continue by describing the regulation of both types of stem cell creams in Europe and in the U.S. Finally, I will give an overview of the major difficulties in the current regulation and conclude with some recommendations.

⁵ <http://www.lancome-usa.com/Absolue-Precious-Cells/1000362,default,pd.html>

⁶ <http://amatokinstore.com/index.php>

⁷ http://www.reviveskincare.com/store/shop/Serums_Peau-Magnifique-Youth-Recruit_prod120041

⁸ http://www.dior.com/beauty/usa/en/skin_care_by_christian_dior_face_care_body_care_su/face-skincare/wrinkle_correction/ridesdaynight/ultimate-wrinkle-restoring-serum/py0535530.html

⁹ http://www.stemcellskincare.com/Stem_Cell_Skin_Care_Serum.htm

¹⁰ <http://www.stemcellfacecream.com>

I. Classification of Stem Cell Creams

Despite their name, so-called “stem cell creams” often do not contain human stem cells. They do, however, claim to influence the stem cells present in the skin of the consumer who applies the cream. I will discuss first this type of cream. After that I will focus on the classification of creams that actually contain human stem cells or stem cell extracts.

A. Creams that Will Influence the Stem Cells in the Skin

(1) The Belgian/European Classification

A facial cream, like the one I will discuss in this section namely one that influences the stem cells in the skin, seems at first sight the typical example of a cosmetic. The Belgian rules on cosmetics (cosmetic products) and drugs (medicinal products) are very similar to the European rules. This is logical as Belgium is a member of the European Union and is therefore both required to implement European Directives and immediately bound by European Regulations.¹¹ An anti-aging cream that influences stem cells in the skin could be qualified as a cosmetic. According to the Belgian *Royal Decree of 15 October 1997 on Cosmetic Products*¹² a “cosmetic product” is “any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, hair, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity

¹¹ A European Directive sets out some goals that Member States need implement by adapting their laws. For more information see http://ec.europa.eu/eu_law/introduction/what_directive_en.htm. A European Regulation has a more direct power and will have binding force in all Member States from the moment they are passed. For more information see http://ec.europa.eu/eu_law/introduction/what_regulation_en.htm.

¹² Art. 1, 1°, Koninklijk Besluit betreffende cosmetica [Royal Decree on Cosmetic Products] of Oct. 15, 1997, BELGISCH STAATSBLAD [B.S.] [Official Gazette of Belgium], Jan. 16, 1998, <http://www.staatsblad.be>: “alle stoffen of mengsels die bestemd zijn om in aanraking te worden gebracht met de verschillende delen van het menselijk lichaamsoppervlak (de opperhuid, de beharing, het haar, de nagels, de lippen en de uitwendige geslachtsorganen) of met de tanden en de mondslimvliezen, uitsluitend of hoofdzakelijk om deze te reinigen, te parfumeren, het uiterlijk ervan te wijzigen en/of de lichaamsgeuren te corrigeren en/of ze te beschermen of ze in goede staat te houden”.

with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odors and/or protecting them or keeping them in good condition”. This definition contains three elements: (1) substance or mixture, (2) the place ON the body where the product will be applied and (2) the *principal purpose* (intended mainly or exclusively) to be a cosmetic product. This is exactly the same definition as can be found in Article 1, 1 of the European *Directive 76/768/EEC of 27 July 1976*¹³ on the *Approximation of the Laws of the Member States relating to Cosmetic Products*.

In the 1970s the EU Member States decided to harmonize their legislation on cosmetics. Free circulation of cosmetics in the EU would finally be possible.¹⁴ The Cosmetics Directive was born. Nonetheless, this directive was recently repealed by *Regulation 1223/2009 of 30 November 2009 on Cosmetic Products*,¹⁵ effective July 11, 2013.¹⁶ A Regulation is a stronger legislative instrument that makes it possible to impose clear and detailed rules that are the same in all Member States and are implemented at the same time in the entire Community.¹⁷ Article 2, § 1 (a) of the Cosmetics Regulation will define cosmetics in the future but the meaning stayed undifferentiated. The intent or principal purpose refers to the presentation of a product from the point of view of a reasonably well-informed consumer. This will be assessed on a case-by-case basis.¹⁸ A cream used on the face to moisturize the skin for the purpose of reducing the appearance of wrinkles, in this case by influencing the

¹³ 1976 O.J. (L 262) 169 [hereinafter Cosmetics Directive].

¹⁴ 1 EUROPEAN COMMISSION, ENTERPRISE DIRECTORATE-GENERAL PHARMACEUTICALS AND COSMETICS, THE RULES GOVERNING COSMETIC PRODUCTS IN THE EUROPEAN 1, 3 (1999), http://www.leffingwell.com/cosmetics/vol_1en.pdf.

¹⁵ 2009 O.J. (L 342) 59 [hereinafter Cosmetics Regulation]. This regulation will come into force on July 11, 2013 with some exceptions that came into force earlier.

¹⁶ With the exception of art. 4b which is repealed with effect from 1 December 2010, *see* art. 38 Cosmetics Regulation.

¹⁷ Recital (2) to the Cosmetics Regulation.

¹⁸ MANUAL ON THE SCOPE OF APPLICATION OF THE COSMETICS 76/768/EEC (ART. 1(1) COSMETICS DIRECTIVE) 1, 11 (6th ed. 2010), http://ec.europa.eu/consumers/sectors/cosmetics/files/doc/manual_borderlines_version06_en.pdf [hereinafter MANUAL].

skin stem cells, has as its principle purpose to change the appearance or protect the skin, or to keep it in good condition. Therefore it seems to be a cosmetic.

Categorizing cosmetics, however, is not that easy. Our cream could be called a “borderline product.”¹⁹ It might fall both within the definition of a cosmetic and a medicinal product.

The Belgian *Law of 25 March 1964 on Medicinal Products* uses an identical definition of medicinal products²⁰ as the European *Directive 2001/83/EC of 6 November 2001 on the Community Code relating to Medicinal Products for Human Use*:²¹

“(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological²², immunological²³ or metabolic²⁴ action, or to making a medical diagnosis.”

¹⁹ Recital 7 to European Directive 2001/83/EC of 6 November 2001 on the Community Code relating to Medicinal Products for Human Use, 2001 O.J. (L 311) 67, mentions « so called borderline products».

²⁰ Art. 1, 1) a Wet op de geneesmiddelen [Law on Medicinal Products] of March 25, 1964, BELGISCH STAATSBLED [B.S.] [Official Gazette of Belgium], April 17, 1964, <http://www.staatsblad.be>: “hetzij fysiologische functies te herstellen, te verbeteren of te wijzigen door een farmacologisch, immunologisch of metabolisch effect te bewerkstelligen, hetzij om een medische diagnose te stellen”

²¹ 2001 O.J. (L 311) 67 [hereinafter Medicinal Products Directive]. This is defined in art. 1, § 2 Medicinal Products Directive.

²² This means the “interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent. Although not a completely reliable criterion, the presence of a dose-response correlation is indicative of a pharmacological effect”. See GUIDANCE DOCUMENT ON THE DEMARCATION BETWEEN THE COSMETIC PRODUCTS DIRECTIVE 76/768 AND THE MEDICINAL PRODUCTS DIRECTIVE 2001/83 AS AGREED BETWEEN THE COMMISSION SERVICES AND THE SERVICES AND THE COMPETENT AUTHORITIES OF MEMBER STATES 1, 9, http://ec.europa.eu/consumers/sectors/cosmetics/files/doc/guidance_doc_cosm-medicinal_en.pdf

²³ This means the action in or on the body by stimulation and/or mobilisation of cells and/or products involved in a specific immune reaction. See *id.*

²⁴ This refers to the action which involves an alteration, including stopping, starting or changing the speed of the normal chemical processes participating in, and available for, normal body function. The fact that a product is metabolised by the human body does not necessarily mean that the substance contained in the product has a metabolic action upon the body. See *id.*

A product can be a medicinal product “by virtue of its presentation” (that is, presented or promoted as having properties for treating or preventing disease in human beings) or “by virtue of function” (may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis).²⁵

For example, if the manufacturer claims that the cream will influence the stem cells in the skin in order to protect the skin from getting older, this would not sufficiently meet the definition of “medicinal product.”²⁶ The following claims on Amatokin Emulsion’s website will therefore not change the product’s classification on their own “the peptide ‘jump starts’ adult skin stem cells to produce new skin cells” or “research shows that as polypeptide #153 is introduced to stem cells, an increase in cell division and thus the production of new skin cells occurs”, etc.²⁷ The cream is not *presented as treating or preventing disease* and therefore cannot be a drug by virtue of its presentation.

The cream can nevertheless be a medicine “by virtue of function” as it may be used in people in order to modify physiological functions in a more than insignificant way²⁸ by exerting a pharmacological action. This does not need to be the *principal purpose* like for cosmetics. A product which reduces cellulite for example may be a medicinal product by virtue of function.²⁹ However, many products that are considered cosmetics modify in fact also physiological functions. Every moisturizing cream will affect the skin cells by adding water to the cells. These products must exercise some effect on somatic skin cells, otherwise

²⁵ MANUAL, *supra* note 18, at 16.

²⁶ The Belgian Federal medicines and Health Products Agency listed some claims that do not make a cosmetic a drug by presentation. See http://www.fagg-afmps.be/nl/binaries/09H002%20positieve%20lijst%20Humaan_tcm290-117288.pdf

²⁷ <http://amatokinstore.com/index.php>

²⁸ Case C-112/89, “Upjohn”, 1991 E.C.R. I-1703.

²⁹ MANUAL, *supra* note 18, at 19.

they are useless.³⁰ All these are however regarded as cosmetics.³¹ This has also been made clear through Article 7a, § 1, g of the Cosmetics Directive that states that the manufacturer of a cosmetic needs to give the competent authority information on the “proof of the effect claimed for the cosmetic product, where justified by the nature of the effect or product”. Article 11, § 2 d of the Cosmetics Regulation stipulates that the “product information file shall contain where justified by the nature or the effect of the cosmetic product, proof of the effect claimed for the cosmetic product”. Having an effect on the human body is undoubtedly not enough to qualify as a drug. The product has to significantly affect metabolism in order to modify the way in which the body functions.³²

If a cream can affect metabolism, it is a medicinal product. Many factors will be considered in making this determination, such as absorption, concentration, route of administration, frequency of application, application site, and the degree of penetration.³³ In addition, the risk to health is an autonomous factor that must be taken into consideration.³⁴ The fact that the same substance is also present in medicinal products as an active ingredient is not decisive. Nevertheless, this may be an indicator of pharmacological, immunological or metabolic action of the substance.³⁵

If the product is categorized as a medicinal product, then it will be exclusively regulated by the laws pertaining to medicinal products. This is called the principle of non-cumulation.³⁶ Therefore, a cream that actually affects the stem cells in the body could

³⁰ GUIDANCE DOCUMENT ON THE DEMARCATION BETWEEN THE COSMETIC PRODUCTS DIRECTIVE 76/768 AND THE MEDICINAL PRODUCTS DIRECTIVE 2001/83 AS AGREED BETWEEN THE COMMISSION SERVICES AND THE SERVICES AND THE COMPETENT AUTHORITIES OF MEMBER STATES 1, 7,

³¹ Recital (7) to the Cosmetics Regulation.

³² Case C-1121/89, “Upjohn“, 1991 E.C.R. I-1703, para 21-22. Affirmed in C-150/00, “Vitamines“, 2004 E.C.R. I-03887, para 65.

³³ MANUAL, *supra* note 18, at 16.

³⁴ C-211/03, C-211/03, C-299/03 to C 318/03 HLH Warenvertriebs GmbH, Orthica BC v Federal Republic of Germany, 2005 E.C.R. I-05141, para 53.

³⁵ MANUAL, *supra* note 18, at 16.

³⁶ This principle is established by the European Court of Justice in Case C-1121/89, “Upjohn“, 1991 E.C.R. I-1703. It is now part of art. 2 (2) Medicinal Products Directive. TREVOR COOK, PHARMACEUTICALS BIOTECHNOLOGY AND THE LAW 301-304 (2009).

possibly be considered a drug by virtue of function, even if not by virtue of presentation. It is important to mention that only the European Court of Justice can give an authoritative interpretation of EU law. This Court and national competent authorities determine on a case-by-case basis whether a product falls within the scope of the Cosmetics Directive or the Medicinal Products Directive.³⁷ The question remains whether these creams have the potential to affect metabolism. In case they do not have these proprieties then the product falls only within the definition of a cosmetic.³⁸

In short, under European law product claims are decisive in determining whether a product falls within the scope of the drug regulation. This is however only the case if the product is expressly indicated or recommended as having therapeutic or prophylactic properties, regardless whether the product has a known therapeutic effect.³⁹ A claim that the cream will influence stem cells in the skin is not enough to consider it a medicinal product. The real properties are decisive in classifying a product as a drug: does the cream modify the physiological function of the skin? Once a product is categorized as a drug, the product cannot also be a cosmetic, and vice versa. For cosmetics the principle purpose of the product determines whether it is a cosmetic or not. This refers to the presentation of the cream and the intent of the manufacturer and is evaluated considering the reasonably well-informed consumer.

³⁷ MANUAL, *supra* note 18, at 2.

³⁸ This can make the product misbranded, *see infra*.

³⁹ C-219/91, “Wilhelmus Ter Voort”, 1992 E.C.R. I-5485, para. 18 and C-227/82, “Van Bennekom”, 1983 E.C.R. 3883, para 18, both with regard to the former, slightly different-worded definition “any substance or combination of substances presented for treating or preventing disease in human beings or animals”.

(2) The United States' Classification

FDA acquired authority over cosmetics in 1938 through the Federal Food, Drug, and Cosmetic Act (FD&C Act).⁴⁰ The FD&C Act states that cosmetics are "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance".⁴¹ Intent refers to the objective intent of the person responsible for the labeling through labeling claims, advertisements⁴², statements, Internet content, or even evidence that the vendor knows that the product is used for that purpose.⁴³ Promotional third party claims or testimonials about the product are also seen as claims that prove intent.⁴⁴ Any claim that a product alters the appearance or feel of the skin would also lead to classification as a cosmetic.⁴⁵

The intended use of the article thus defines the category in both Belgium and the EU. Skin moisturizers fall under this definition as does any material intended for use as a component of a cosmetic product.⁴⁶

⁴⁰ Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301 et seq.

⁴¹ FD&C Act, § 201 (i), 21 U.S.C. § 321.

⁴² Advertisements itself are also regulated. For this paper I however will not discuss them in detail. Art. 87 of Medicinal Products Directive (which repealed Council Directive 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use 1992, O.J. (L 113) 13–18) prohibits advertising of medicinal products for which no marketing authorizations has been granted and art. 88 prohibits ads for the general public for prescription-only medicinal products. (See e.g. COOK, *supra* note 36, at 312.) Belgium implemented this in its Law on Medicinal Products. Direct-to-consumer ads are therefore not allowed in the EU.

The Federal Trade Commission Act (FTCA) enforced by the Federal Trade Commission (FTC) covers unfair or deceptive practices (15 U.S.C. § 5) in advertisements on cosmetics⁴² and OTC products. Prescription drug ads are regulated by FDA. Ads are not only printed but also on TV and the internet. (See e.g. Peter Barton Hutt, Richard A. Merrill, Lewis A. Grossman, *Food and Drug Law, Cases and Materials* 809 (2007); Wen Schroeder, *Cosmeceutical (Antiaging) Products: Advertising Rules and Claims Substantiation*, in 2 GLOBAL REGULATORY ISSUES FOR THE COSMETICS INDUSTRY 121, 134 (Karl Lintner ed., 2009)

⁴³ 21 C.F.R. § 201.128. Also consumer perception because of the product's reputation and ingredients with a well known therapeutic use can establish the necessary intent for a drug. See e.g. Peter Barton Hutt, *The Legal distinction in the United States between a cosmetic and a drug*, in COSMECEUTICALS 223 (Peter Elsner & Howard I. Maibach eds., 2000).

⁴⁴ See e.g., *United States v. Vital Health Products, Ltd.*, 786 F. Supp. 761, 776 (E.D. Wis. 1992), *aff'd*, 985 F.2d 563 (7th Cir. 1993).

⁴⁵ Repeated in *United States v. "Sudden Change,"* 288 F. Supp. 29 (E.D.N.Y. 1968). This case was however reversed because the claim was not only about altering the appearance. See *infra* note 56; Hutt, *supra* note 43, at 232.

⁴⁶ Is it a Cosmetic, a Drug, or Both?,

<http://www.fda.gov/Cosmetics/GuidanceComplianceRegulatoryInformation/ucm074201.htm>

Inspired by the European situation, we also want to look into the regulation of drugs under U.S. law. The FD&C Act defines drugs as "*articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease*" and "*articles (other than food) intended to affect the structure or any function of the body of man or other animals*".⁴⁷ The intent is defined in the same way as for cosmetics.⁴⁸ For example a claim that a product revitalizes cells, although marketed as a cosmetic, will establish the intended use to be a drug.⁴⁹ That is not a superficial effect anymore. Consumer expectations play a role too: although a fluoride toothpaste manufacturer only claimed that the toothpaste keeps teeth attractive, a typical cosmetic claim, the intended use is implied by the known effects of the ingredients of the product.⁵⁰ Here we see an important difference compared to the European regulation. In the definition for drugs in the U.S., "intent" plays an important role, whereas Europe focuses more on the proprieties of the products themselves, unless the product is represented as having therapeutic or prophylactic properties ("may be used..." in Europe compared to "intended to use..." in U.S.).

Products can be regulated as both cosmetics and as drugs if they have more than one intended use.⁵¹ As mentioned before, this is not possible in Europe where the non-cumulation rule applies. A moisturizer for example is intended to alter the appearance, promoting attractiveness or beautifying. It is therefore a cosmetic. If the manufacturer claims the product will affect the structure or function of the skin in *removing* the wrinkles, the cream becomes a drug. For cosmetics only superficial effects are allowed.⁵² If this is the case, the requirements for both cosmetics and drugs have to be fulfilled. In the popular literature these products are sometimes called "cosmeceuticals": a combination of "cosmetics" and "pharmaceuticals."

⁴⁷ FD&C Act, § 201(g)(1): "Also articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them", are considered drugs.

⁴⁸ See Senate report: S. REP. NO. 361, 74th Cong., 1st Sess. § 201 (1935).

⁴⁹ Is it a Cosmetic, a Drug, or Both?, *supra* note 46.

⁵⁰ Jacqueline A. Greff, *Regulation of cosmetics that are also drugs*, 51 FOOD & DRUG L.J. 243, 255 (1996).

⁵¹ Hutt, *supra* note 43, at 223; See also e.g. Is it a Cosmetic, a Drug, or Both?, *supra* note 46.

⁵² Schroeder, *supra* note 42, at 126.

This is nonetheless not a term recognized by the FD&C Act.⁵³ Today it has been made clear by court decisions and FDA's interpreting materials that for example a lip softener is a cosmetic but a lip balm for chapped lips is also a drug; a skin moisturizer is a cosmetic, but a wrinkle remover is a (non-prescription⁵⁴) drug as well; a deodorant is a cosmetic but an antiperspirant is a drug.⁵⁵

The wrinkle remover cases of the 1960s provide some great examples.⁵⁶ Claims of a facial cream like "face-lift without surgery" and "super-active" were considered to be drug claims⁵⁷ like "restructures and repairs skin"⁵⁸. Claims are often not that clear and many factors will be taken into account such as the overall impression of the advertisement.⁵⁹ In 1987 FDA issued warning letters to firms saying that "cell recovery", "cell repair", "increased collagen production", "restructuring the deepest epidermal layers" were all drug claims.⁶⁰

On March 1, 2011 Jaba Labs received a warning letter by FDA. StemCellin Intensive Emulsion and StemCellin Deep Wrinkle Serum StemCellin® are both facial creams that claimed on their website to "activate your own skin stem cells", "delays deterioration of essential skin cells", "reverses chronological aging", etc. FDA stated that the creams are therefore "promoted for uses that cause them to be drugs under section 201(g)(1)(C) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 321(g)(1)(C)]." The claims establish that these products are drugs because they are structure/function claims.⁶¹

⁵³ Hutt, *supra* note 43, at 223.

⁵⁴ *See infra*.

⁵⁵ For more examples *see* Hutt, *supra* note 43, at 228; Schroeder, *supra* note 42, at 131.

⁵⁶ *United States v. "Line Away,"* 284 F. Supp. 107 (D. Del. 1968), *aff'd*, 415 F.2d 369 (3d Cir. 1969); *United States v. "Sudden Change,"* 288 F. Supp. 29 (E.D.N.Y. 1968), *rev'd*, 409 F.2d 734 (2d Cir. 1969); *United States v. "Helena Curtis Magic Secret,"* 331 F. Supp. 912 (D. Md. 1971).

⁵⁷ *United States v. "Sudden Change,"* 409 F.2d at 742. (2d Cir. 1969).

⁵⁸ *Estee Lauder*, 727 F. Supp. 1.

⁵⁹ Greff, *supra* note 50, at 269.

⁶⁰ Gary L. Yingling & Michael A. Swit, *Cosmetic Regulation*, in *FOOD AND DRUG LAW* 366 (Food & Drug Law Inst. ed., 1991).

⁶¹ Warning letter FDA to JABA LABS, March 1, 2011, <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm246086.htm>

(3) Conclusion

The U.S. and Europe each classify cosmetics based on the intent. A cream that claims to influence stem cells in the skin could be a cosmetic in both jurisdictions, at the least as long as in Europe the physiological functions of the skin are not altered. In the U.S. the claim is the only factor that can make a cosmetic also a drug. In Europe the principle of non-cumulation applies which means that a product cannot be in both classes. In Europe, claims are also crucial for drugs but only if the claim relates to therapeutics or therapeutic or prophylactic properties. Otherwise the function of the product, not the presentation is decisive. This implies that a cream that affects stem cells in the skin would be a drug in Europe because of its function, regardless of the claim. In the U.S., however, this same cream would be seen as a cosmetic unless it were claimed that the cream affected the structure or function of the skin (e.g. “activate your own skin stem cells”), in which case it would also be a drug.

B. Creams Containing Human Stem Cells or Stem Cell Extracts

(1) The Belgian/European Classification

A skin moisturizer containing human stem cells or stem cell extracts is placed on external parts of the human body for the purpose of changing the appearance of the skin or to keep the skin in good condition. It could therefore be qualified as a cosmetic product according to current and future Belgian and European rules as long as it does not alter the function of the body. This is nevertheless not the end of the story.

Article 2 of the Cosmetics Directive stipulates that cosmetic products “*must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use*”. According to article 3 of the European Regulation 1223/2009 “*a cosmetic product made available on the market shall be safe for human health when used under normal or reasonably foreseeable conditions of use*”.⁶² These articles make clear that cosmetics are considered in Europe to be something that needs to be regulated in order to be safe. For thousands of years, cosmetic products only contained ingredients derived from natural sources such as plants, minerals and animals. Safety was not a significant concern. Nowadays synthetic ingredients have entered the field and increased the potential risks.⁶³ Fortunately, in practice cosmetic products only very rarely cause health hazards. This does however not mean that they are safe. Cosmetics may be used extensively for a long period of time. That is why Europe decided to regulate the ingredients of cosmetic products.⁶⁴

⁶² Art.2, 2° e) Royal Decree 15 October 1997 refers to data that have to be collected concerning risks for human health when the use of cosmetics is both under normal or reasonably foreseeable conditions.

⁶³ SCCNFP, SCCNFP'S NOTES OF GUIDANCE FOR TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION, 0690/03 (5th ed. October, 20, 2003) 1, http://ec.europa.eu/health/archive/ph_risk/committees/sccp/documents/out242_en.pdf; these notes give guidance authorities and cosmetic industry for better and harmonized compliance with the Cosmetics Directive and its amendments.

⁶⁴ The First control of ingredients happened because of Council Directive 93/35/EEC of 14 June 1993 amending for the sixth time Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products, 1993 O.J. (L 151) 32.

Safety evaluation was first carried out by the Scientific Committee on Cosmetology (SCC).⁶⁵ In 1997 the Scientific Committee on Cosmetics and Non-Food Products Intended for Consumers (SCCNFP) was established by the Commission Decision 97/579/EC. The committee answered questions from the Commission and gave advice on cosmetics and non-food products. The advisory guidelines promulgated by this committee were compulsory.⁶⁶ Beginning in 2008 the Scientific Committee on Consumer Safety (SCCS) was established by Commission Decision 2008/721/EC of 5 September 2008. The SCCS functions as an advisory structure of Scientific Committees and experts in the field of consumer safety, public health and the environment. According to the preamble to the *European Regulation 1223/2009* (62) the Commission has to be assisted by the SCCS, an independent risk assessment body. The SCCS is responsible for reviewing ingredients and assessing conditions for safe use. The results of these reviews are subsequently published.

Is a cream with stem cells or stem cell extracts on the ingredients list safe? Both the Belgian Royal Decree⁶⁷ and the Cosmetics Directive (and the Cosmetics Regulation)⁶⁸ which will replace the Directive after July 11, 2013 state that “cells, tissues or products of human origin” are not allowed in cosmetics. This important exception has been added to the list of substances prohibited in cosmetics by the *Eighteenth Commission Directive 95/34/EC of 10 July 1995 adapting to technical progress Annexes II, III, VI and VII to Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products*.⁶⁹ The reason for this directive is that cells, tissues or products of human origin can

⁶⁵ The Scientific Committee on Cosmetology (SCC) was founded on 19 December 1977 by Commission Decision 78/45/EEC in order to assist the European commission in drawing and amending European Union directives and regulations on cosmetic products. See SCCNFP, OPINIONS 1997-2004, CLASSIFICATION OF SUBSTANCES AS INGREDIENTS OF COSMETIC PRODUCTS 3, http://ec.europa.eu/health/archive/ph_risk/committees/sccp/documents/out242_en.pdf

⁶⁶ Ar. 8.2. Cosmetics Directive.

⁶⁷ Annex art. N2, n° 416 Royal Decree on Cosmetic Products.

⁶⁸ Annex II, List of prohibited substances in cosmetic products, n°416 Cosmetics Directive and Regulation.

⁶⁹ 1995 O.J. (L 167) 19.

transmit the Creutzfeldt-Jakob disease, human spongiform encephalopathy, and certain virus diseases such as human immunodeficiency virus (HIV). Given the state of scientific knowledge in 1995 up until now, it seemed necessary to prohibit human cells, tissues and other products in cosmetics under the “precautionary principle.”⁷⁰ The SCCNFP of the European Commission stated that only “substances for which data at the time of assessment support the conclusion that they do not pose a health hazard” may be used in cosmetics. In case substances are dangerous for health according to available data or the data do not justify the assumptions that they are safe, they cannot be used as ingredients in cosmetics.⁷¹ This was already the position of the SCC, as stated on October 4, 1994 to prohibit the use of human tissues and extracts in cosmetics.⁷² Therefore, it appears that stem cells or stem cell extracts are not safe or at the least not proven to be safe for use in cosmetics.

In brief, a cream containing human stem cells or products derived from human stem cells is considered by European authorities not safe enough to enter the market. Compliance with the regulation for cosmetics even does not offer enough safety. The cream is therefore not a cosmetic and does not need to follow the regulation pertaining to cosmetics. This of course does not permit manufacturers to market these products free from control. Creams with stem cells/extracts may be considered medicinal products. Stem cells in a cream do not cause

⁷⁰ Preamble Eighteenth Commission Directive 95/34/EC of 10 July 1995 adapting to technical progress Annexes II, III, VI and VII to Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products. The principle implies that when “there are reasonable grounds for concern for the possibility of adverse effects but scientific uncertainty persists, provisional risk management measures based on a broad cost/benefit analysis whereby priority will be given to human health and the environment” may be adopted, See ELIZABETH, JUDITH JONES & RENE VON SCHOMBERG, IMPLEMENTING THE PRECAUTIONARY PRINCIPLE: PERSPECTIVES AND PROSPECTS (2006).

⁷¹ SCCNFP, OPINIONS 1997-2004, SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD PRODUCTS INTENDED FOR CONSUMERS - THE CLASSIFICATION OF SUBSTANCES ADOPTED BY THE SCCNFP DURING THE 11TH PLENARY MEETING OF 17 FEBRUARY 2000, http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/sccnfp_opinions_97_04/sccp_out110_en.htm

⁷² SCCNFP, OPINIONS 1997-2004, OPINION CONCERNING AMINO ACIDS OBTAINED BY HYDROLYSIS OF HUMAN HAIR, June 28, 2000, http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/sccnfp_opinions_97_04/sccp_out122_en.htm

problems this time. Substances in a drug can be of human origin.⁷³ If a stem cell cream against wrinkles for anti-ageing can be used to correct or modify physiological functions by exerting a pharmacological action, it might be classified as a medicinal product in Belgium and Europe. This is only in case the cream has a significant effect on the physiological functions of the body. If the cream works as a normal cream it will not be a drug and it can therefore in my opinion not be marketed in Europe.

It is now interesting to see how a cream containing stem cells will be classified in the U.S.

(2) The United States' Classification

As mentioned above, the U.S. uses the “intent” requirement to qualify cosmetics, as does Europe. Facial creams are therefore usually cosmetics. In the U.S. FDA only prohibits eleven cosmetic ingredients compared to 1328 in the Cosmetics Regulation in Europe.⁷⁴ Cells from human origin are not in the list of prohibited substances in the U.S. At first glance there is therefore no reason why a cream containing stem cells/extracts from stem cells could not be considered a cosmetic.

In the U.S. drugs are classified according to the claims made⁷⁵ whereas Europe focuses more on the properties of the product itself. This difference can have important consequences.

A facial cream containing stem cell extracts will not be considered a drug in the U.S. as long as the manufacturer does not claim it is intended to use *in the diagnosis, cure, mitigation, treatment, or prevention of disease* or to *affect the structure or any function of the*

⁷³ Art. 2 Law on Medicinal Products, art. 1, 3 Medicinal Products Directive.

⁷⁴ www.national-toxic-encephalopathy-foundation.org/cirpro.pdf. In the GUIDE TO INSPECTIONS OF COSMETIC PRODUCT MANUFACTURERS, <http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074952.htm>, FDA adds 5 more ingredients that are prohibited.

⁷⁵ See Senate report: S. REP. NO. 361, 74th Cong., 1st Sess. § 201 (1935).

body of man or other animal. When the website of Swiss Apple Stem Cell Serum alleges that the product “boosts the production of human skin stem cells, protects human skin stem cells from stress, thus decreasing wrinkles and producing younger, fresher looking skin”, this makes the product a drug.⁷⁶ In Europe as mentioned before, only if the cream alters the function of the body will it be considered a drug. A facial cream containing human stem cells or stem cell extracts, claiming to influence the existing stem cells in the skin, so that the existing stem cells will be activated, can be considered not only a cosmetic but also a drug in the U.S. based on that claim.⁷⁷ These products are then intended to affect the function of the body. This is the case regardless of whether there are stem cells in the cream and whether the cream actually works. Perhaps surprisingly, it is not the ingredients but the claims that determine the applicable regulation. In reality however, FDA will often decline to classify a product as a drug, despite of the almost drug claim, as long as it has no drug efficacy or the product is proven to be safe.⁷⁸

FDA bases its classification sometimes on the ingredients and sometimes on the risk of the product.⁷⁹ It seems indeed not logical that an ingredient that might be unsafe can be put in a topically-applied product as cosmetic as long as the manufacturer does not claim that it is a drug.⁸⁰ It is however not true that the mere use of the ingredient makes it a drug. The use of active pharmaceutical ingredients (APIs) can lead to the classification of a product as a drug when the ingredient is so closely identified with therapeutic properties that using the term in

⁷⁶ http://www.stemcellskincare.com/Stem_Cell_Skin_Care_Serum.htm

⁷⁷ Warning letter FDA to JABA LABS, March 1, 2011, <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm246086.htm>

⁷⁸ A product can be considered safe without going through the drug procedure if it is a nonprescription drug. *See infra*. Cosmetic Products Containing Certain Hormone Ingredients: Notice of Proposed Rulemaking, 58 Fed. Reg. 47,611 (1993).

⁷⁹ Discussed in Greff, *supra* note 50, at 243.

⁸⁰ Robert P. Giovacchini, *The Significance of the Over-the-Counter Drug Review with Respect to the Safety Considerations of Cosmetic Ingredients*, 30 FOOD DRUG COSM. L.J. 223 (1975).

the label or just in the ingredients list makes it a drug claim.⁸¹ This argument was used by FDA for cases in which the ingredients had only drug functions or the ingredients at higher concentrations could only have drug effects. This is nonetheless never discussed in court.⁸² For example with cosmetics containing hormones, FDA first defined using the term “hormone” as an implied drug claim. A new drug application approval was therefore necessary, unless the hormones had been proven to be safe.⁸³ In the latter case the hormones could also be used in cosmetics without triggering regulation as a drug.⁸⁴

FDA also classified some products as drugs based on the risk they cause to consumers. Absent promotional drug claims, a product may be deemed a drug because of actual physical effects.⁸⁵ This is however not always a sign of the objective intent because it is possible that the manufacturer decided to put the product on the market despite of the side-effect and not because of the drug effect. Courts will most likely not uphold this argument as it is contrary to the statute.⁸⁶ Another reason according to some why this classification might not be upheld is that (almost) all cosmetics penetrate the skin which means they all affect the structure or function of the body.⁸⁷ I think nonetheless that this interpretation is not convincing. All cosmetics seek to create a certain effect or they would not be marketed. As long as the effect is superficial one could say it stays a cosmetic. If a product alters, repairs or renews the skin, even only temporarily, then there is a drug. This would be the case in Europe too. Claims are therefore not the only possibility as a criterion to classify products. For now the U.S. still uses the *claim* that the structure or function of the body is affected to make the product a drug, not

⁸¹ United States v. Articles of Food and Drug, 444 F. Supp. 266, 271 (E.D. Wisc. 1978).

⁸² Greff, *supra* note 50, at 254-255.

⁸³ *See infra*.

⁸⁴ 58 Fed. Reg. 47,608 and 47,611.

⁸⁵ Greff, *supra* note 50, at 255-256.

⁸⁶ Greff, *supra* note 50, at 256.

⁸⁷ Hutt, *supra* note 43, at 227.

the effect itself. For example, a product that claims to even temporarily repair or renew skin would be classified as a drug.⁸⁸

(3) Conclusion

Creams based on stem cells or extracts from stem cells are not treated the same everywhere. In Europe they do not fall within the regulation of cosmetics because of safety risks, but they can be cosmetics in the U.S. In case there is a structure/function claim also the drug regulation has to be applied in the U.S. In Europe the cream can be regulated as a drug, but only if it has a significant effect on the physiological functions of the body. Otherwise the cream cannot be marketed.

⁸⁸ Hutt, *supra* note 43, at 232.

II. Stem cell creams regulated

A. Regulation in Belgium/Europe

A cream influencing stem cells in the skin, without containing stem cells from humans is a cosmetic if it does not change the function of the body. It is a medicinal product if it does change that function. For the latter regulation I refer to the explanation in part (2). I will discuss first the regulation concerning cosmetics.

(1) Creams Claiming to Influence the Stem Cells in the Skin Without Affecting the Function of the Skin: Cosmetics

Cosmetics can only be manufactured in Belgium or imported in Belgium from outside of the European Union if the following criteria are met.⁸⁹

1. The responsible person (the person who lets the product enter the market for the first time or who manufactures it) notifies the competent authority or “CA” (the Federal medicines and Health Products Agency in Belgium)⁹⁰ of its activities before entering the cosmetic enters the

⁸⁹ The Royal Decree on Cosmetic Products informs us that there are four major steps in order to be sure cosmetics are safe.

⁹⁰ Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu (FAGG/AFMPS)

market. An “activity” can be, for example, information on where the dossier in point 4, *infra*, is available.⁹¹

The manufacturer in Belgium must also notify the CA of its activities in Belgium as a manufacturer of the product before entering the market and must notify the CA afterwards annually.⁹²

2. The labeling complies with the requirements: warnings,⁹³ not misleading,⁹⁴ etc.⁹⁵

3. The responsible person handed over the formulas to the poison centre not less than forty-eight hours before the product enters the market, and must do so again each time the formula changes.⁹⁶

4. The responsible person keeps a dossier with all data on the product.⁹⁷ The following are among the data that have to be included in the dossier:

- the composition of the product;
- detailed lists of the building blocks of the product and of the finished product;
- the method of manufacturing;

⁹¹ Art. 2, 1° Belgian Royal Decree 15 October 1997 and art. 7,4 Cosmetics Directive, art. 13 Cosmetics Regulation asks the responsible person (manufacturer, importer, distributor, etc see art. 4) to notify the Commission.

⁹² Art. 2, 1°bis Belgian Royal Decree 15 October 1997 and art. 7,4 Cosmetics Directive, art. 13 Cosmetics Regulation asks the responsible person (manufacturer, importer, distributor, etc *see* art. 4) to notify the Commission.

⁹³ Art. 5, §1, 3° and annex 3 and 8 Belgian Royal Decree of 15 October 1997, annexes of Cosmetics Directive and Regulation.

⁹⁴ Labels see art. 6, 1° and Belgian Royal Decree 15 October 1997; art. 6, 3 Cosmetics Directive; art. 20, 1 Cosmetics Regulation.

⁹⁵ Art. 4, 1° and Belgian Royal Decree 15 October 1997; art. 2 Cosmetics Directive; art. 3 b and 19 Cosmetics Regulation.

⁹⁶ Art. 2, 5° Belgian Royal Decree 15 October 1997 and only in Cosmetics Regulation the responsible hands the information over to the commission which will inform the poison centre.

⁹⁷ Art. 2, 2° Belgian Royal Decree 15 October 1997; art. 7 a 1 Cosmetics Directive and art. 11 Cosmetics Regulation.

- safety control about the effects of the product on human's health through risk assessment by a safety assessor: as long as the cosmetic is found to be safe for use,⁹⁸ the cream will not be rejected by the safety assessor.⁹⁹

The rules explained above show that safety of cosmetics in Europe is determined by qualified and experienced safety assessors. Data from the UK prove that this is a quick and effective assessment and ensures consumer safety.¹⁰⁰ This is combined with good manufacturing practices which need to be followed in order to manufacture cosmetics so the end user will not be harmed.¹⁰¹

Contrary to drugs (*see infra*) which can only contain substances listed in a compendium or ingredients that are explicitly supported,¹⁰² cosmetics can normally contain any ingredient not otherwise restricted or prohibited.¹⁰³ Even if all ingredients of a particular product are allowed, the final product can be unsafe and therefore will not have the required safety stamp and cannot be allowed to enter the market.¹⁰⁴ The labeling requirements are also different. A true premarket approval is not in use but premarket notification on the other hand is a requirement through which the safety assessor can reject the product as not safe.¹⁰⁵ In the very improbable case that the manufacturer decides to put the product on the market even though it is declared unsafe, Article 18 of the Law of 24 January 1977 on Consumer Health

⁹⁸ Under the umbrella requirement in art. 4, 1° Royal Decree of 15 October 1997; art. 2 Cosmetics Directive and article 3 Cosmetics Regulation.

⁹⁹ Art. 3, §2, 1° Belgian Royal Decree of 15 October 1997; art. 7a 1 e) Cosmetics Directive; art. 10, 2 Cosmetics Regulation.

¹⁰⁰ Betton, *supra* note 1, at 18-19.

¹⁰¹ Rudolf A. Overbeek and Roel Pekay, *Restricted Substances in Consumer Products: the Challenge of Global Chemical Compliance*, in *supra* note 1, at 71, 80. See for example art. 7,a, 1, C) Cosmetics Directive and art. 3, 3° Royal Decree on Cosmetic Products.

¹⁰² Janet Winter Blaschke, *Regulatory Developments in Canada, Japan, Australia, China, and India*, in *supra* note 1, at 21, 32; *see e.g.* art. 5 a Cosmetics Directive.

¹⁰³ Annex II prohibited, annex III restricted use of the applicable legislation.

¹⁰⁴ The umbrella requirement in art. 4, 1° Royal Decree of 15 October 1997, art. 2 Cosmetics Directive and article 3 Cosmetics Regulation.

¹⁰⁵ Art. 25 Cosmetics Regulation.

Protection¹⁰⁶ will apply: the products are considered dangerous for human's health and the Competent Authority can take actions to prevent the product from entering the market. The Competent Authority will, once on the market "require the responsible person to take all appropriate measures, including corrective actions bringing the cosmetic product into conformity, the withdrawal of the product from the market or its recall, within an expressly mentioned time limit." Fines and imprisonment are also possible punishments if the responsible person does not comply.¹⁰⁷

Where a cream falsely claims to influence the stem cells in the skin, the cream will be considered a cosmetic. Cosmetic products, however, may not make claims that are untrue, and the responsible person would therefore need to change the claim. From the moment the cream has a significant effect on metabolism it will be considered a drug.

(2) Creams Containing Human Stem Cells or Stem cell Extracts and
Influencing Stem Cells in the Skin or Creams Influencing Stem Cells in the
Skin that Affect the Function of the Skin: Drugs

A stem cell cream that contains human stem cells cannot be classified as a cosmetic product under current European regulations. Therefore, the cream will be regulated as a drug.

In order to obtain marketing authorization in the EU, the Commission on the recommendation of the European Medicines Agency (EMA) or a national competent authority¹⁰⁸ (in Belgium, this is the Federal Medicines and Health Products Agency) determines whether to grant a marketing application after consideration of the submitted

¹⁰⁶ Wet betreffende de bescherming van de gezondheid van de gebruikers op het stuk van de voedingsmiddelen en andere producten [Law on Consumer Health Protection] of January 24, 1977, BELGISCH STAATSBAD [B.S.] [Official Gazette of Belgium], April 8, 1977, <http://www.staatsblad.be>

¹⁰⁷ Artt. 19 and 20 Law on Consumer Health Protection.

¹⁰⁸ Art. 6 Medicinal Products Directive.

dossier.¹⁰⁹ Quality, safety and efficacy are factors that will be taken into consideration before market authorization can be awarded. Article 8, 3, (i) shows that for example results of pharmaceutical (physico-chemical, biological or microbiological) tests, pre-clinical (toxicological and pharmacological) tests and clinical trials have to be submitted. This is only possible after the clinical trial application is approved.¹¹⁰ Irrespective of the procedure¹¹¹ that has to be followed, applying for marketing authorizations is a very time consuming procedure. Companies creating stem cell creams will not try to enter the European market as this regulation is too strict for them to be profitable.

There is also an ongoing obligation to carry out post-market surveillance, called “pharmacovigilance.”¹¹² Inspections are part of the competent authority’s power.¹¹³

If a product such as Peau Magnifique actually does what is claimed on its website, namely, dramatically increase skin cell renewal, this would be proof that the product is a drug by virtue of function if it were marketed in Europe.¹¹⁴ However, in most cases products cannot live up to such unrealistic claims. In that case a product will be classified as a cosmetic, but as a cosmetic it would not comply with all requirements, such as labels that are not misleading and proof of the claimed effect. The competent authority would in Europe therefore ask to bring the product into conformity or to withdraw the product from the market. A recall is another option. Otherwise fines and imprisonment are possible.¹¹⁵

(3) Conclusion

¹⁰⁹ SALLY SHORTHORSE, GUIDO TO EU PHARMACEUTICAL REGULATORY LAW 33 (2010), COOK, *supra* note 36, at 283 *et seq.*

¹¹⁰ <http://www.pharmainfo.net/reviews/new-drug-approval-process-regulatory-view>

¹¹¹ Centralized, decentralized, mutual recognition or national procedure. *See* SALLY SHORTHORSE, GUIDO TO EU PHARMACEUTICAL REGULATORY LAW 47 *et seq.* (2010).

¹¹² Artt. 21 to 29 European Regulation No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, 2004 O.J. (L 136) and artt. 101 to 108 Medicinal Products Directive.

¹¹³ Art. 111 Medicinal Products Directive.

¹¹⁴ http://www.reviveskincare.com/store/shop/Serums_Peau-Magnifique-Youth-Recruit_prod120041

¹¹⁵ *See supra.*

The rules concerning cosmetics are less stringent than those for drugs for which, for example, premarket authorization rather than premarket notification is necessary¹¹⁶ and only ingredients in a compendium or explicitly supported ingredients are allowed.¹¹⁷ Both cosmetics and drugs need to comply with (different) good manufacturing practices. However, this does not mean that cosmetics are not regulated enough in Europe. A cream that does not contain stem cells but claims to influence stem cells will be required to comply with cosmetic rules if the claim is untrue, but possibly the drug rules would apply if the claim were true. A false cosmetic claim will not be allowed and the claim needs to be changed. A cream containing stem cells will always need to follow the more stringent drug rules of tests followed by marketing application. In most cases, this will not be profitable because, first, it is a time consuming procedure to get approval, and second, the cream needs to be effective (the claim needs to be true). In most cases, this means that the cream will probably not be put on the market.

B. Regulation in the United States

A cream with human stem cells as ingredients or a cream that influences the stem cells in the skin are regulated in the same way as long as they claim to have the same effects. First I'll discuss the cream when there is not a structure/function claim. Then I'll discuss it when there is a structure/function claim.

(1) Creams Influencing Stem Cells in the Skin and/or Containing Human Stem Cells or Stem Cell Extracts Without Structure/Function Claim: Cosmetics

¹¹⁶ Betton, *supra* note 1, at 18-19.

¹¹⁷ Blaschke, *supra* note 102, at 32.

See e.g. art. 5 a Cosmetics Directive.

The “Colors and Cosmetics” division within FDA’s Center for Food Safety and Applied Nutrition (CFSAN) regulates cosmetics.¹¹⁸ This makes cosmetics the only product of significance under FDA’s authority without a center of its own in FDA.¹¹⁹ It is therefore no surprise that cosmetics are regulated much more leniently than any other product under its authority.¹²⁰

Cosmetic products and ingredients (except for color additives) do not need to get FDA’s premarket approval (which is the case for most drugs *see infra*) and are not subject to safety or efficacy testing, or good manufacturing practices (although there was in the past an initiative to create good manufacturing practices (GMPs) for cosmetics, this idea has never been acted upon¹²¹).¹²² The “Safe Cosmetics Act of 2010”¹²³ would have required cosmetic companies to register the company and its products with FDA, fully disclose ingredients in products and share safety data, etc. However, the bill never became law.

Safety is now still only assured through the rules concerning adulteration and misbranding in the FD&C Act, the label requirements in the FPLA Act and some administrative regulations. A warning label is mandatory in case the safety is not adequately substantiated.¹²⁴ This scheme works well according to some, because cosmetics are by nature generally low risk and because of industry self-regulation.¹²⁵ Moreover, FDA is not equipped to investigate all potential situations but must allocate its resources in a way that focuses on the most life-threatening public health issues. Cosmetics often do not cause serious adverse

¹¹⁸ Schroeder, *supra* note 42, at 123.

¹¹⁹ Greff, *supra* note 50, at 248.

¹²⁰ Peter Barton Hutt, Richard A. Merrill, Lewis A. Grossman, *Food and Drug Law, Cases and Materials* 49 (2007).

¹²¹ Greff, *supra* note 50, at 246.

¹²² Greff, *supra* note 50, at 243.

¹²³ H.R. 5786, 111th Cong. (2009-2010).

¹²⁴ Schroeder, *supra* note 42, at 123.

¹²⁵ Greff, *supra* note 50, at 243.

effects compared to food, drugs or medical devices.¹²⁶ Cosmetics are only regulated through the Center for Food Safety and Applied Nutrition.¹²⁷ In case there is a safety problem concerning cosmetics, it is not predictable when they will react.¹²⁸

The FD&C Act prohibits both adulteration, which takes into account the composition of the product and the container and how it is manufactured and shipped (sec. 601), and misbranding, which focuses on the representation of the product (sec. 602) for products in interstate commerce (sec. 301).

The introduction or delivery for introduction into *interstate commerce* of any cosmetic that is adulterated or misbranded is prohibited. The adulteration or misbranding in interstate commerce itself is not allowed. The receipt in interstate commerce of such a cosmetic and the delivery or proffered delivery thereof for pay or otherwise is also prohibited. Not only is it prohibited to engage in any of the above actions but also the causing of these actions is prohibited. (sec. 301)

Interstate commerce is a requirement that is almost always fulfilled as it applies to all different steps in a product's manufacture, packaging and distribution. Although there are certain exemptions,¹²⁹ factors such as these generally cause the requirements of the FD&C Act to apply to your products.¹³⁰

A cosmetic is *adulterated* if it:¹³¹

- contains poisonous or deleterious substance that may render it injurious to users; (a)

¹²⁶ Schroeder, *supra* note 42, at 138.

¹²⁷ Greff, *supra* note 50, at 248.

¹²⁸ Harold I. Zeliger, *Cosmetics: Toxicity and Regulatory Requirements in the US*, in *supra* note 1, at 63, 69.

¹²⁹ 21 C.F.R. § 701.9

¹³⁰ Key Legal Concepts,

<http://www.fda.gov/Cosmetics/GuidanceComplianceRegulatoryInformation/ucm074248.htm>

¹³¹ FD&C Act, § 601, 21 U.S.C. § 361; Greff, *supra* note 50, at 248-249.

- contains a filthy, putrid, or decomposed substance; (b)
- has been prepared, packed, or held under insanitary conditions; (c)
- contains an unapproved color additive (not applicable to hair dyes) (d) or
- is in a container composed of a poisonous or deleterious substance that may render it injurious (e).

Let us take a closer look at Lifeline's skin serums.¹³² Recall that these creams contain stem cells extracts derived from human oocytes. They could therefore be considered adulterated in the U.S. because stem cells of human origin are considered deleterious substances that may render the cream dangerous for consumer's health. The European regulation for example made clear that cells from human origin are prohibited. One could therefore conclude they are not safe. This is nevertheless not always true.

On the one hand, many chemicals listed in the Annexes to the European regulations will never be used in cosmetics, such as aircraft fuel. This argument is nonetheless not applicable here because the stem cell extracts are used in cosmetics. On the other hand the chance that a product will truly be absorbed by the skin and cause harm is not high. The epidermis is waterproof and relatively non-permeable (if intact), therefore the formulation of the drug is very important to reach the deeper layers and pass the epidermal layer.¹³³ In addition, experts state that growth factors and enzymes are notoriously temperature-sensitive. In order to work "ingredients would have to remain stable for weeks or months at room temperature, get past the epidermal layer, go into the right cells, and exert the proper stimulation once reaching

¹³² <http://www.lifelineskincare.com/>

¹³³ If the cream would contain full stem cells, the next problem is then keeping the stem cells at their place. For this it relies on cell signaling and various properties of the tissue such as stiffness. Another problem would be the viability of stem cells in a cream. A product sold as cosmetic off-the-shelf would not guarantee to contain stem cell extracts in the end. See e.g. Dennis E. Discher, Paul Janmey & Yu-li Wang, *Tissue Cells Feel and Respond to the Stiffness of Their Substrate*, 310 SCIENCE 1139 (November 18, 2005).

their destination”.¹³⁴ If all that would occur, the cream would be an adulterated cosmetic. If these properties are in addition claimed, the product would become a drug, with all regulatory consequences.¹³⁵ The chance that Lifeline’s skin serums would be considered an adulterated cosmetic because they contain human stem cell extracts seems therefore negligible. Important however in this discussion is a study carried out by the Cosmetic Ingredient Expert Panel on human products in cosmetics.¹³⁶ “Different materials called Human Placental Extracts and Placental Extracts, assumed to contain estrogenic hormones or other biologically active substances, are not recognized as cosmetic ingredients, even though the use of these ingredients in cosmetics has been reported to the Food and Drug Administration (FDA).”¹³⁷ The conclusion of the research was that the available data were insufficient to support safety for use in cosmetics.¹³⁸ In short it seems that these serums are adulterated cosmetics and FDA could act upon it (*see infra*). However FDA does not act. In my opinion this means that change is clearly necessary. I have another argument to support this.

The same cream, but this is even true without stem cells as ingredients, can also be adulterated if the substance that would influence the stem cells in the skin is not safe. If the cream really works and influences skin stem cells, this actually influences the structure or function of the skin and therefore is more hazardous than a normal cosmetic. Although no drug claim was made in my example, I think that it would be better for consumer’s safety if

¹³⁴ Bryan Nelson, *A superficial success*, NATURE REPORTS STEM CELLS (January 15, 2009), <http://www.nature.com/stemcells/2009/0901/090115/full/stemcells.2008.163.html>

¹³⁵ *See infra* for drugs regulation.

¹³⁶ B. Nair, AR Elmore, *Cosmetic Ingredient Review Expert panel, Final report on the safety assessment of human placental protein, hydrolyzed human placental protein, human placental enzymes, human placental lipids, human umbilical extract, placental protein, hydrolyzed placental protein, placental enzymes, placental lipids, and umbilical extract*, 21 INT J TOXICOL. 81-91 (2002).

¹³⁷ « The additional data needed include (1) skin sensitization at concentration of use; (2) gross pathology and histopathology in skin and other major organ systems associated with repeated exposures, and dermal reproductive and developmental toxicity data; (3) photosensitization; (4) one genotoxicity assay in a mammalian system; if positive, then a 2-year dermal carcinogenicity study using National Toxicology Program (NTP) methods may be needed; (5) ocular toxicity, if available. »

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the drug regulation would apply, which is in Europe the case. As a practical result this would probably drive these manufacturers away from the market.

Cosmetics are on the other hand *misbranded* if:¹³⁹

- its labeling is false or misleading (a);
- its labeling fails to contain the name and address of the manufacturer, packer, or distributor and an accurate statement of the quantity of its contents (b);
- its labeling fails to include any required information (c);
- its container is made, formed, or filled so as to be misleading (d);
- its packaging or labeling violates the Poison Prevention Packaging Act of 1970 (f) or
- it is a color additive that violates the packaging and labeling requirements under section 721. (e)

A cosmetic is misbranded when the label does not bear the required information and warnings or is false and misleading.¹⁴⁰ The terms label and labeling are the same for different products under FDA's authority: labeling refers to "all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article". A label is "the display of written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article".¹⁴¹ Any promotional material, even

¹³⁹ FD&C Act, § 602, 21 U.S.C. § 362; Greff, *supra* note 50, at 249.

¹⁴⁰ Schroeder, *supra* note 42, at 124.

¹⁴¹ Section 201 k and m FD&C Act.

on the Internet, can be considered a label.¹⁴² A label is false or misleading when the claim contained therein is false or misleading.¹⁴³ If our cream, however, falsely states that it can influence stem cells in the skin, it can be construed as misbranded but the misbranding arises under the drug regulation, not the cosmetics regulation (*see infra*).

The Fair Packaging and Labeling Act (FPLA)¹⁴⁴ is another statute through which the FDA can regulate cosmetics, including and our cream.¹⁴⁵ The FPLA requires a full ingredient declaration in order to enable consumers to make informed purchases. In the event a cosmetic violates the FPLA requirements, it will also be considered misbranded under the FD&C Act.

¹⁴⁶

In addition to the above statutes, there are also a wide variety of applicable regulations.¹⁴⁷ For example, some ingredients are prohibited (*see supra*). All other ingredients can be used as long as the finished cosmetic is safe, the label is in compliance with regulations and the ingredient does not cause the cosmetic to be adulterated or misbranded.¹⁴⁸ A cosmetic that is shown to be unsafe, without a warning on the label that the safety of the product has not been determined, can be regarded as misbranded.¹⁴⁹

FDA is not the only actor regulating cosmetics; the industry actively uses self-regulation too. For example, the cosmetic industry is not only controlled by FDA but also by the

¹⁴² Schroeder, *supra* note 42, at 125.

¹⁴³ United States v. Johnson, 221 U.S. 488 (1911).

¹⁴⁴ 15 U.S.C. § 1451 et seq.

¹⁴⁵ FDA Authority over Cosmetics,

<http://www.fda.gov/Cosmetics/GuidanceComplianceRegulatoryInformation/ucm074162.htm>

¹⁴⁶ *Id.*; 21 C.F.R. § 701.2 provides labeling compliance information, see also

Zeliger, *supra* note 128, at 65.

¹⁴⁷ Zeliger, *supra* note 128, at 65.

¹⁴⁸ FDA Authority over Cosmetics, *supra* note 145.

¹⁴⁹ 21 C.F.R. § 740.10 (a) explains this warning statement: “that a cosmetic ingredient or product that has not been adequately substantiated for safety prior to marketing be conspicuously labeled “Warning -- The safety of this product has not been determined.”

Personal Care Products Council (PCPC), which was previously the trade association, Cosmetic, Toiletry and Fragrance Association (CTFA). CTFA was established in 1976 by the voluntary Cosmetic Ingredient Review (CIR) in order to control the safety of cosmetics' ingredients.¹⁵⁰ CIR Expert Panel results are published in the International Journal of Toxicology and on the CIR website. This procedure is comparable to the European SCCS, although the latter is mandatory. CIR's findings are not binding.¹⁵¹ An example is the cosmetic ingredients compendium of the CIR in 2009. As highlighted earlier, human placental protein, human placental enzymes, human placental lipids and human umbilical extract were classified as "insufficient data to support safety".¹⁵² Like Lifeline's skin serums, discussed above, a product like Stemixx which contains human umbilical stem cell extracts is therefore not proven to be safe. Nevertheless, the product is sold in the U.S. as CIR's reports are not compulsory for FDA to follow.

Similarly, registration of establishments is not required but possible (Voluntary Cosmetic Registration Program¹⁵³ 21 C.F.R. 710 and 720); nor is filing data on ingredients or adverse events related to cosmetics.

On the one hand, this does not mean FDA has no power at all to react. FDA can take regulatory action against an adulterated or misbranded cosmetic. FDA can inspect cosmetic manufacturing facilities in order to find out whether cosmetics are adulterated or misbranded under the FD&C Act or FPLA.¹⁵⁴ FDA collects samples during plant inspections, follow-up to complaints of adverse reactions (CAERS), etc. Research on cosmetic products and

¹⁵⁰ Greff, *supra* note 50, at 245-246.

¹⁵¹ Greff, *supra* note 50, at 246.

¹⁵² http://www.cir-safety.org/staff_files/PublicationsListDec2009.pdf

¹⁵³ Voluntary Registration of Cosmetic Product Establishments, 39 Fed. Reg. 10,059 (1974) (codified at 21 C.F.R. § 710); Voluntary Filing of Cosmetic Product Ingredient and Cosmetic Raw Material Composition Statements, 39 Fed. Reg. 10,060 (1974) (codified at 21 C.F.R. § 720); Voluntary Filing of Cosmetic Product Experiences, 39 Fed. Reg. 10,062 (1974) (codified at 21 C.F.R. § 730).

¹⁵⁴ Voluntary Registration of Cosmetic Product Establishments, 39 Fed. Reg. 10,059 (1974) (codified at 21 C.F.R. § 710); Voluntary Filing of Cosmetic Product Ingredient and Cosmetic Raw Material Composition Statements, 39 Fed. Reg. 10,060 (1974) (codified at 21 C.F.R. § 720); Voluntary Filing of Cosmetic Product Experiences, 39 Fed. Reg. 10,062 (1974) (codified at 21 C.F.R. § 730).

ingredients is also part of FDA's actions. Moreover, from the moment these products enter the market, enforcement actions are still possible.¹⁵⁵ Through the Department of Justice in the federal court system, FDA can even try to remove these cosmetics from the market. In order to prevent continued shipping of the product, a restraining order from a district court is also useful. These products can be seized as well. Criminal action is another possibility in the fight against a person who violates the law.¹⁵⁶ Another incentive to comply is that the industry too benefits from the continued sale of safe products.

On the other hand, FDA does not have the power to recall an unsafe cosmetic. A manufacturer can decide to opt for market withdrawal or recall (in instances of a violation of the FD&C Act).¹⁵⁷ Companies are also not required to register their cosmetic establishments, file data on ingredients or report cosmetic-related injuries to FDA (like, for example, as is necessary for nonprescription drugs, *see infra*). It is important to note that FDA's decision to take regulatory actions is "based upon agency priorities, consistent with public health concerns and available resources".¹⁵⁸ FDA enforcement therefore is not that common in this area of law and cosmetics are often not a priority.¹⁵⁹ Even with scarce resources, preventive actions are, in my opinion, preferable and cheaper than reacting after the fact.

Today, Europe and the U.S. ensure a bilateral cooperation through a confidentiality agreement entered into on 2 July 2007, which enables them to exchange confidential information about the safety of cosmetics such as post-marketing data; and the multilateral cooperation through a regulatory dialogue called "International Cooperation on Cosmetic

¹⁵⁵ FDA Authority over Cosmetics, *supra* note 145.

¹⁵⁶ FDA Authority over Cosmetics, *supra* note 145.

¹⁵⁷ 21 C.F.R. §§ 7.40 through 7.59.

¹⁵⁸ FDA Authority over Cosmetics, *supra* note 145.

¹⁵⁹ Schroeder, *supra* note 42, at 138.

Regulation" (ICCR) with Japan and Canada as well¹⁶⁰. I think the time has come to harmonize the regulation of cosmetics. At this time, if our cream is considered a pure cosmetic, the regulation is clearly less stringent than in the European Union where the cream containing stem cells and the cream influencing the stem cells in the skin would follow the drug regulation. Even the cosmetic rules itself are more lenient in the US than in Europe. There is neither mandatory premarket notification nor safety or efficacy testing: there is no safety control laid out by FDA, no adverse events need to be filed and the companies do not need to be registered. FDA could however react against an unsafe cosmetic when it is adulterated or misbranded but FDA's policy does not make cosmetics their priority and therefore FDA often does not act.

(2) Creams Influencing Stem cells in the Skin and/or Containing Human Stem Cells or Stem Cell Extracts, Both With Structure/Function Claim: Cosmetic and Drug¹⁶¹

When the cream is both a cosmetic and a drug, not only the cosmetic but also the drug requirements have to be fulfilled. This is important as the requirements for these two categories of products differ substantially in the U.S.¹⁶²

In addition to the elements listed for cosmetics, a drug is *adulterated* if:¹⁶³

¹⁶⁰ See

<http://europa.eu/rapid/pressReleasesAction.do?reference=IP/07/1024&format=HTML&aged=0&language=EN&guiLanguage=en>

¹⁶¹ Greff, *supra* note 50, at 243.

¹⁶² Hutt, *supra* note 43, at 223.

¹⁶³ FD&C Act, § 501, 21 U.S.C. § 351. These elements make a cosmetic adulterated and are also factors that make drugs adulterated (§ 501) (*see supra* for cosmetics): contains poisonous or deleterious substance that may render it injurious to users (a) (2) (C); contains a filthy, putrid, or decomposed substance (a) (1); has been prepared, packed, or held under insanitary conditions (a) (2) (A); contains an unapproved color additive (not applicable to hair dyes) (a) (4) or is in a container composed of a poisonous or deleterious substance that may render it injurious (a) (3); Greff, *supra* note 50, at 249.

- it has not been manufactured, processed, packed, and held in conformity with current good manufacturing practices; (a) (2) (B)
- its strength, quality, or purity does not meet compendial standards; (b)
- its strength, quality, or purity does not meet purported standards (c) or
- it has been mixed or packed with any substance that reduces its quality of strength. (d)

In addition to the factors I summed up for cosmetics, a drug product is *misbranded* if:¹⁶⁴

- it is not labeled with the established name of the drug, the active ingredient(s), adequate directions for use, and adequate warnings (e);
- it is manufactured, prepared, propagated, compounded, or processed in an unregistered establishment (o);
- it is a nonprescription drug marketed in the U.S. and on the label there is no domestic address or domestic phone number to send a report of serious adverse event to (x) or
- the responsible person (who submitted the drug application) fails to comply with requirements (z).

Because cosmetics in general are considered to cause less risks to health, the rules are less stringent than for drugs, which are seen as inherently risky. This is already clear from the longer list of factors that could cause a drug to be classified as misbranded or adulterated. For

¹⁶⁴ FD&C Act, § 502, 21 U.S.C. § 352. These elements make a cosmetic adulterated and are also factors that make drugs misbranded (§ 502) (*see supra* for cosmetics): its labeling is false or misleading (a); its labeling fails to contain the name and address of the manufacturer, packer, or distributor and an accurate statement of the quantity of its contents (b); its labeling fails to include any required information (c); its container is made, formed, or filled so as to be misleading (i); its packaging or labeling violates the Poison Prevention Packaging Act of 1970 (p) or it is a color additive that violates the packaging and labeling requirements under section 721 (m); Greff, *supra* note 50, at 249.

example, drugs need in general the IND/NDA procedure for approval. Preclinical toxicological testing, clinical testing under an investigational new drug application (IND), submission of a new drug application (NDA) to get FDA approval and post-approval requirements, like good manufacturing practices, are all mandatory.¹⁶⁵ A drug is regulated differently depending on its type in the U.S.: prescription or nonprescription (also known as over-the-counter - OTC). It is therefore important to discuss both classes. Prescription drugs cannot be OTC drugs because they are either toxic or harmful, or only safe under the supervision of a doctor.¹⁶⁶ In general, a new drug will need a New Drug Application (NDA) in order to enter into interstate commerce. There is an exception in case the drug is Generally Recognized as Safe and Effective (GRAS/E). In the Drug Amendments of 1962, Congress mandated that all drugs, including OTC drugs, be reviewed for effectiveness.¹⁶⁷ FDA then created the OTC monograph system. Drugs were reviewed and could be classified as GRAS/E upon review by expert panels.¹⁶⁸ From 1972 to 1983, reports were indeed established by advisory review panels of experts that evaluated the safety and effectiveness of OTC drugs' active ingredients and reviewed the labels. When the "OTC Drug Review" was finished, a report was sent to the Commissioner of FDA, who would publish as last step in the procedure, the final monographs. All reports were published in 1983 although not all monographs are final yet.¹⁶⁹ These monographs, which are published in the Federal Register, contain requirements for categories of nonprescription drugs, such as what ingredients may be used and for what intended use. The benefit of this system is that drugs falling within an OTC monograph (thus considered GRAS/E) did not need to get NDA approval. In turn, when

¹⁶⁵ Peter Barton Hutt, Richard A. Merrill, Lewis A. Grossman, Food and Drug Law, Cases and Materials Chapter IV (2007).

¹⁶⁶ FD&C Act, § 503 (b).

¹⁶⁷ Peter Barton Hutt, Richard A. Merrill, Lewis A. Grossman, Food and Drug Law, Cases and Materials 788 (2007).

¹⁶⁸ 21 C.F.R. § 330.

¹⁶⁹ Peter Barton Hutt, Richard A. Merrill, Lewis A. Grossman, Food and Drug Law, Cases and Materials 798 (2007).

ingredients do not fall within a monograph that states that it is GRAS/GRAE, they need to get NDA before entering the market.

The monograph system for OTC drugs makes it possible to approve products in a short period of time. Cosmetic drugs such as our cream could be seen as OTC drugs, now that the OTC Drug Review has been reformed in 1997.¹⁷⁰ If the effects and active ingredients and labels fall within an OTC monograph, the cosmetic would be an OTC drug and not a prescription drug.¹⁷¹ No pre-approval is necessary then. The manufacturer only needs to request monograph status for the product. Stem cells nevertheless might not fall within an existing OTC monograph. This would mean that the stem cells in the cream would make it a prescription drug if there are also structure/function claims. The premarket NDA approval procedure is then the only possibility. Although my main conclusion seems to be that the U.S. under-regulates our cream, the situation is different here. I do see this as overregulation for the cream that only claims to influence the stem cells in the skin but that has no proof that it actually does. In Europe, this would still be classified as a cosmetic. Here it would probably be considered a prescription drug (*see infra* on Jaba Labs). On the other hand, I have to admit that the manufacturer would easily avoid this problem by removing the claim. I, however, do not see this as overregulation for the cream containing human stem cell extracts. In Europe, a similar cream would follow the same approval procedure.

It is not true that an OTC drug, now it does not need to get the NDA approval, is not sufficiently regulated. Production facilities must be listed with FDA.¹⁷² Besides reporting

¹⁷⁰ 62 Fed. Reg. 23350 (April 30, 1997); Hutt, *supra* note 43, at 230.

¹⁷¹ Greff, *supra* note 50, at 251.

¹⁷² FD&C Act, § 510.

product related injuries to FDA, production facilities must meet stringent drug GMP procedures.¹⁷³ FDA facility inspections are even a part of the regulation.¹⁷⁴

FDA can also send regulatory letters to the company.¹⁷⁵ An example is the Warning Letter Jaba Labs received about its products StemCellin Intensive Emulsion and StemCellin Deep Wrinkle Serum StemCellin®. These are both facial creams that claimed on their website to “activate your own skin stem cells”, “delays deterioration of essential skin cells”, “reverses chronological aging”, etc. FDA stated that the claims establish that these products are drugs because they are structure/function claims.¹⁷⁶ As a drug, the product was not seen as GRAS/E. Only with NDA approval could they market the way they did. They were therefore adulterated.

The prescription drug approval procedure often takes a decade or more and is also very costly.¹⁷⁷ Many cosmetic manufacturers will therefore decide not to invest in it. Did this mean that the stem cell cream had to leave the market unless it started an NDA? No. FDA already referred to another solution. It declared that the labeling and other claims were not in compliance with the applicable laws and regulation. It was therefore an example of a misbranded drug. The drug claims made the creams drugs that failed to comply with the drug labeling requirements.¹⁷⁸ The violations should be promptly corrected. Otherwise seizure or injunctions could follow. In reality, the manufacturer changed the website.¹⁷⁹ For FDA's purposes, this is sufficient. This means that a potentially unsafe product can stay on the market in the U.S. as long as the manufacturer changes its claims.

¹⁷³ 21 C.F.R. §§ 210 and 211. Failure to follow GMP requirements causes a drug to be adulterated [FD&C Act, § 501(a)(2)(B)].

¹⁷⁴ Greff, *supra* note 50, at 251.

¹⁷⁵ Hutt, *supra* note 43, at 231-232.

¹⁷⁶ Warning letter FDA to JABA LABS, March 1, 2011, <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm246086.htm>

¹⁷⁷ Hutt, *supra* note 43, at 227.

¹⁷⁸ Yingling, *supra* note 60, at 365-367.

¹⁷⁹ <http://www.stemcellfacecream.com>

Two of FDA's rationales to classify a product as a drug are to ensure safety and to prevent the use of ineffective ingredients in products that come off as drugs.¹⁸⁰ Classifying them as drugs is an important measure given that FDA does not control the safety of cosmetics in the same way. Although most cosmetic drugs avoid pre-approval requirements by conforming to the requirements in an (OTC) drug monograph, in the case of Jaba Labs this was not possible.¹⁸¹ FDA's dual goals are clearly not met through the current practice where companies have the option of simply modifying the claims they make with respect to the drugs. An example of a product that does not want to fall within the scope of the drug regulation is Dior's R60/80 Xp. It claims on its website that "wrinkles *seem*¹⁸² IMMEDIATELY smoothed, INTENSELY reduced after 1 month, LASTINGLY restored after 3 months".¹⁸³ Amatokin, however, used to make claims such as "rejuvenates the skin and makes you look younger ... a lot younger" in the past and found itself facing legal repercussions as these claims were not scientifically proven. Today, these claims have been removed from their website.¹⁸⁴ The problem is thus solved for the FDA and Amatokin, but not for the consumers in terms of their safety. If the product is seen to be as hazardous as it was previously at the time the claims were made, the consumers' health remains in jeopardy.

(3) Conclusion

A cosmetic that claims to work into the skin's stem cells would be qualified as a drug in the U.S. Adjusting the claim is an easy way to comply with the rules (as the cosmetic would then no longer be misbranded or adulterated) while concurrently avoiding the strict(er)

¹⁸⁰ Margaret Gilhooley, *Cosmetic Regulation: Going Beyond Appearance*, SEVENTY-FIFTH ANNIVERSARY COMMEMORATIVE VOLUME OF FOOD AND DRUG LAW 323, 323-24 (Food & Drug Law Inst. ed., 1984).

¹⁸¹ Greff, *supra* note 50, at 243 and 253.

¹⁸² Emphasis added.

¹⁸³ http://www.dior.com/beauty/usa/en/skin_care_by_christian_dior_face_care_body_care_su/face-skincare/wrinkle_correction/ridesdaynight/ultimate-wrinkle-restoring-serum/py0535530.html

¹⁸⁴ <http://www.cosmeticsdesign.com/Product-Categories/Cosmeceuticals/Stem-cell-cream-gets-into-marketing-trouble>

drug regulations. Case closed for FDA but the product is still the same and therefore, could be injurious.

In Europe this is not possible. The claim would only make the cream a drug if the effects are proven to be scientifically true. Even if it stays classified as a cosmetic, the safety of the product is assured as Europe does have safety assessment requirements for cosmetics. The U.S. lacks such mandatory cosmetic safety regulations and therefore, underregulates creams containing stem cell extracts that are prohibited from being classified as cosmetics in Europe.

III. Conclusion and Recommendations

Cosmetics have changed over time. New innovations have altered the possible ingredients and effects of these products. Some companies produce creams with so-called properties of working on the consumer's body's stem cells. If these claims are true, the product could potentially be hazardous. An even more urgent matter concerns the ingredients of cosmetics. In the U.S., almost all ingredients are allowed to be used in cosmetics. Human cell (extracts) can contain many diseases if not handled carefully. By allowing creams containing human stem cells to be marketed with no mandatory safety assessment, the U.S. continues to put its citizens in jeopardy.

In my opinion, the goal is to put only safe cosmetics on the market. I think this can only be achieved if there is a mandatory safety assessment with (arguably) a list of prohibited or restricted ingredients. This is already the situation in Europe.

A drawback of this rule could be that manufacturers become unwilling to offer the product or alternatively, that the products' prices skyrocket. This could lead to less innovative

cosmetics. Nevertheless, a choice has to be made and in my view, safety ought to be treated as priority number one. Based on my analysis of stem cell creams, I view that FDA's regulation of cosmetics is insufficient to protect consumers against today's new innovations. In the U.S., an example of a solution to this problem would be to extend premarket safety requirements to apply to cosmetics, as is currently done in Europe. Premarket authorization, as is currently required for drugs, would not be necessary.¹⁸⁵

Moreover, it seems almost unbelievable that something as trivial as the wordings on a website can change the rules applicable in the U.S. from a very lenient set of regulations to very strict regulations ... and back. This implies that creams that are potentially hazardous would almost always fall between the cracks and escape safety regulation altogether. In Europe, however, a product that could be injurious will need to follow the rigorous, expensive and time consuming drug regulations. Claims have no influence on the products discussed in this paper, but the cream's properties do.

I think the dual division between cosmetics and drugs in the U.S. is sufficient. A third category of so called cosmeceuticals or borderline products should not get different regulation (as for instance is the case in Japan¹⁸⁶). A dual division is acceptable but the criterion, *i.e.* solely on the basis of claims by manufacturers, on which this happens is not. Let superficiality be used to explain how a product has to be applied but let it not rule a decision as important as the applicable regulatory category: drug or cosmetic.

¹⁸⁵ Hutt, *supra* note 43, at 237.

¹⁸⁶ Kenkichi Oba, *Drugs versus cosmetics: cosmeceuticals?*, in COSMECEUTICALS 241 (Peter Elsner & Howard I. Maibach eds., 2000).

